United States Court of Appeals for the Federal Circuit

05-1157

AMGEN INC.,

Plaintiff-Appellee,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals Inc.)
and TRANSKARYOTIC THERAPIES, INC.,

Defendants-Appellants.

DECIDED: August 3, 2006

Before MICHEL, Chief Judge, CLEVENGER, Senior Circuit Judge, and SCHALL, Circuit Judge.

Opinion for the court filed by Circuit Judge SCHALL. Dissenting-in-part opinion filed by Chief Judge MICHEL.

SCHALL, Circuit Judge.

This is a patent case. Amgen, Inc. ("Amgen") is the owner of U.S. Patent Nos. 5,547,933 ("the '933 patent"), 5,618,698 ("the '698 patent"), 5,621,080 ("the '080 patent"), 5,756,349 ("the '349 patent"), and 5,955,422 ("the '422 patent"). The patents are directed to recombinant deoxyribonucleic acid ("DNA") technology relating to the production of the hormone erythropoietin ("EPO"). All five patents share a common

specification and descend from Application No. 06/561,024 ("the '024 application"), filed on December 13, 1983.

In April of 1997, Amgen brought a declaratory judgment action against Hoechst Marion Roussel, Inc. (now known as Aventis Pharmaceuticals Inc.) ("HMR") and Transkaryotic Therapies, Inc. ("TKT") (collectively, "HMR/TKT") in the United States District Court for the District of Massachusetts, alleging that HMR/TKT's Investigational New Drug Application ("INDA") for an EPO product infringed the five patents. In January of 2001, following a Markman hearing, summary judgment proceedings, and a bench trial, the district court issued an opinion in which it: (i) construed the disputed claims; (ii) held the patents not unenforceable; (iii) held the asserted claims of the '080, '349, and '422 patents not invalid and infringed with the exception of claim 7 of the '349 patent, which it found not infringed; (iv) held the asserted claims of the '698 patent not infringed; and (v) held the asserted claims of the '933 patent not infringed or, in the alternative, invalid for failure to satisfy 35 U.S.C. § 112. Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69, 165–66 (D. Mass. 2001) ("Amgen I").

In Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313 (Fed. Cir. 2003) ("Amgen II"), we affirmed in toto the district court's claim construction. We also affirmed (i) the court's determination that none of the patents at issue is unenforceable by reason of inequitable conduct; (ii) its contingent determination that the asserted claims of the '933 patent are invalid under section 112; (iii) its grant of summary judgment that claim 1 of the '422 patent is infringed; (iv) its determination that the '933, '698, '080, and '349 patents are not anticipated by U.S. Patent No. 4,377,513 ("the Sugimoto patent"); and

(iv) its determination that claims 1, 3, 4, and 6 of the '349 patent are infringed. Id. at 1320.

However, we vacated (i) the district court's determination that the asserted claims of the '933 patent are not infringed; (ii) its determination that Dr. Eugene Goldwasser's clinical study, described in Dr. Goldwasser's grant application entitled "Erythropoietin: Purification, Properties, Biogenesis" ("the Goldwasser reference"), and the Sugimoto patent do not anticipate claim 1 of the '422 patent; (iii) its determination that the Sugimoto patent does not render claim 1 of the '422 patent obvious; (iv) its determination that claims 2-4 of the '080 patent are not invalid and are infringed under the doctrine of equivalents; (v) its determination that the asserted method claims of the '698 patent are not rendered obvious by the Sugimoto patent and are not infringed; and (vi) its determination that the Sugimoto patent does not render claims 1, 3, 4, 6, and 7 of the '349 patent invalid and that claim 7 of the '349 patent is not infringed. Id.

We remanded the case to the district court to do the following: (i) construe the term "therapeutically effective amount" in claim 1 of the '422 patent and then determine whether either the Goldwasser reference or the Sugimoto patent anticipates claim 1 or whether the Sugimoto patent renders claim 1 obvious, id. at 1354, 1356, 1358; (ii) determine whether the Sugimoto patent renders claims 2-4 of the '080 patent obvious and whether, as far as claims 2-4 are concerned, Amgen can rebut the presumption of the surrender of equivalents and thus assert infringement of those claims under the doctrine of equivalents, id. at 1345, 1358; (iii) determine whether the Sugimoto patent renders claims 4-9 of the '698 patent obvious and whether claims 4-9 are infringed, id. at 1357, 1358; and (iv) determine whether the Sugimoto patent renders claims 1, 3, 4,

6, and 7 of the '349 patent obvious and whether claim 7 of the '349 patent is infringed, id. at 1357, 1358.

The case is now back before us following proceedings on remand in which the district court construed the term "therapeutically effective amount" in claim 1 of the '422 patent and conducted a further bench trial. See Amgen, Inc. v. Hoechst Marion Roussel, Inc., 339 F. Supp. 2d 202 (D. Mass. 2004) ("Amgen III Validity & Literal Infringement Judgment"); Amgen, Inc. v. Hoechst Marion Roussel, Inc., 287 F. Supp. 2d 126 (D. Mass. 2003) ("Amgen III Doctrine of Equivalents Judgment"). Based upon various findings and rulings, the court entered judgment in favor of Amgen as follows: (i) claim 1 of the '422 patent is not invalid, Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 334, 336; (ii) claims 2-4 of the '080 patent are not invalid, id. at 336, and Amgen is not estopped from asserting infringement of claims 2-4 under the doctrine of equivalents because it rebutted the presumption of surrender of equivalents, Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 160; (iii) claims 4-9 of the '698 patent are not invalid and are literally infringed, Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 336; (iv) claims 1, 3, 4, 6, and 7 of the '349 patent are not rendered obvious by the Sugimoto patent, id. at 325, 336, and claim 7 of the '349 patent is literally infringed, Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 336.

On appeal, HMR/TKT challenges all of the above rulings. Our disposition of the appeal is as follows:

(i) Because we hold that the district court erred in its construction of the term "therapeutically effective amount" in claim 1 of the '422 patent, we vacate the judgment

of the district court that claim 1 is not invalid. We remand the case to the district court for a determination as to whether the Goldwasser reference anticipates claim 1 under a revised claim construction. (ii) We reverse the judgment of the district court that HMR/TKT's accused product infringes claims 2-4 of the '080 patent under the doctrine of equivalents. We do so because we hold that the district court erred in ruling that Amgen rebutted the presumption that, during prosecution, it surrendered coverage to EPO with a 165-amino acid sequence, which is the sequence of HMR/TKT's product. Because claims 2-4 of the '080 patent are not infringed, it is unnecessary for us to address HMR/TKT's alternative argument by way of an affirmative defense that claims 2-4 are anticipated by the Goldwasser reference. (iii) We affirm the judgment of the district court that claims 4-9 of the '698 patent are not invalid and are literally infringed. (iv) We affirm the judgment of the district court that claim 7 of the '349 patent is not invalid and is literally infringed. Thus, we affirm-in-part, reverse-in-part, vacate-in-part, and remand.[1]

BACKGROUND

I.

As noted, the patents at issue relate to recombinant DNA technology for the production of EPO. EPO, which is a naturally occurring hormone, stimulates the production of red blood cells in the bone marrow through a process called erythropoiesis. Thus, the production of EPO is useful in treating blood disorders

[1] Even though we do not agree with all of the district court's rulings in this case, we note the court's careful and thorough opinions in both Amgen III Validity & Literal Infringement Judgment and Amgen III Doctrine of Equivalents Judgment.

characterized by low hematocrit, which is a low ratio of red blood cells to total blood cells. The production of EPO in usable amounts was made possible by Amgen's team led by Dr. Fu-Kuen Lin, who first successfully identified the EPO DNA sequence. See '422 patent, col. 20, ll. 28-33. Amgen markets and sells its EPO product under the brand name "Epogen."

DNA is the genetic material of all living things.[2] Id. col. 1, ll. 28-29. DNA is composed of a series of subunits, called nucleotides, that are linked together to form a linear polymeric form—a strand. Id. col. 1, ll. 33-35. Each nucleotide contains one of four nitrogen-containing ring compounds, called bases. The bases fall into two categories: pyrimidines, which include cytosine ("C") and thymine ("T"), and purines, which include adenine ("A") and guanine ("G"). Id. col. 1, ll. 35-46; James D. Watson et al., Molecular Biology of the Gene 98 (5th ed. 2004); Bruce Alberts et al., Molecular Biology of the Cell 63, 120 (4th ed. 2002). The sequence of A, T, G, and Cs on a strand of DNA forms what is known as a "DNA sequence." DNA is double-stranded, such that two complimentary strands are linked together. '422 patent, col. 1, ll. 35-42.

Genetic information is expressed through the production of proteins, which are molecules containing long chains of amino acids. Alberts, supra, at 129. Ribonucleic acid ("RNA") determines the composition of proteins. Watson, supra, at 31; see also Alberts, supra, at 301. During a process called transcription, DNA is used to make messenger RNA ("mRNA") with the sequence corresponding to the DNA sequence of A,

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[2] The basics of recombinant DNA technology are set forth in Amgen I and, to a lesser extent, in Amgen II. We repeat here only the points necessary for an understanding of the issues presented in this appeal.

T, G, and Cs coding for a particular gene.[3] '422 patent, col. 1, ll. 42-43, 49-51. Transcription of the gene is prompted by a promoter, a sequence of DNA that initiates transcription. Id. col. 2, ll. 4-6. The promoter is typically located upstream of the gene to be transcribed.[4] Id. After transcription is completed, the mRNA non-coding sequences, called introns, are spliced out and the mRNA coding sequences, called exons, are spliced together. The mRNA sequence is then translated by ribosomes to form a protein composed of amino acids. Amgen III Doctrine of Equivalents Judgment, 287 F. Supp. 2d at 145.

The common specification of Amgen's patents describes how Dr. Lin combined his discovery of the DNA sequence for EPO with recombinant DNA technology to make EPO-producing cells. In order to create these EPO-producing cells, Dr. Lin made an expression vector carrying the EPO DNA sequence he had discovered. '422 patent, col. 11, ll. 1-10. An expression vector is a circular piece of DNA on which a desired gene may be coded. See id. Figs. 2-4, col. 2, ll. 36-54. In addition to the desired gene, an expression vector may also contain a marker and a promoter site. See id. col. 3, ll. 35-37, col. 25, ll. 33-36. The expression vector incorporates itself into a host cell's genetic code. The promoter then triggers the host cell to transcribe mRNA

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[3] As the name "messenger" implies, mRNA transcripts are intermediates in the process of protein synthesis. Transcription of mRNA from DNA is completed in the nucleus of the cell. After it undergoes additional processing in the cell's nucleus, the complete mRNA is exported to the cell's cytoplasm, where it guides the synthesis of proteins. See Alberts, supra at 304-05, 327-28.

[4] "Upstream" refers to the location of a particular segment of the genetic sequence on a strand of DNA in relation to a particular gene. For example, if a segment is "upstream" of a particular gene and transcription proceeds in a completely linear order along the DNA sequence, then the segment will be transcribed before the gene.

corresponding to the genetic code encoded on the vector. See id. col. 2, ll. 30-35. This mRNA is then translated into a protein by the host cell. Id. The marker in the expression vector enables scientists to identify the cells that successfully incorporated the desired gene. Id. col. 25, ll. 64-66. The DNA inserted into the genetic code of the host cell through the expression vector is characterized as exogenous DNA because it is not "native" to the host cell. Genetic recombination using exogenous DNA is referred to as heterologous recombination. Id. col. 1, l. 53–col. 2, l. 3.

The expression vector described in Example 10 of the common specification of Amgen's patents contains Dr. Lin's EPO DNA sequence, a selectable dihydrofolate ("DHFR") marker, and a promoter 44 base pairs upstream of the EPO DNA sequence. Id. col. 24, l. 17, col. 25, 36-40. When exposed to Chinese hamster ovary ("CHO") cells, Dr. Lin's expression vectors integrate themselves into the DNA of the host CHO cells. Id. col. 25, ll. 58-66. The general disclosures in the background section of the '422 patent describe how promoters, like the one used in Example 10, prompt host cells to transcribe mRNA corresponding to exogenous genes such as the EPO and DHFR genes in Example 10. See id. col. 1, ll. 53-56, col. 25, ll. 64-66. In the invention of the five patents, prior to production of a protein from the mRNA with the sequence coding for EPO, the mRNA sequence is spliced to remove introns and to connect exons. After splicing, the mRNA is translated into the 166-amino acid protein shown in Figure 6 of the common specification of the patents.

Prior to secretion from the cell, the 166-amino acid EPO protein undergoes cleaving. In this process, the final amino acid in the sequence shown in Figure 6 of the

'422 patent, arginine, is cleaved off, leaving a 165-amino acid protein. This 165-amino acid protein is then secreted as mature human EPO by the cell.

II.

HMR and TKT collaborated to develop a drug known as HMR4396. HMR4396 consists of human EPO produced from TKT's R223 cell line grown in culture. Amgen I, 126 F. Supp. 2d at 98. The R223 cell line produces human EPO through the use of a viral promoter that prompts transcription of the human EPO gene. In order to create the R223 cell line, HMR/TKT transfected human tumor cells with the viral promoter. This viral promoter is located far upstream of the EPO gene in the R223 cells. Because the viral promoter is not "native" to the human tumor cells, the R223 promoter is considered exogenous DNA. However, the R223 cells are described as using homologous or endogenous recombination because the human EPO gene that the viral promoter controls is "native" to the cells.

III.

Amgen filed suit for a declaratory judgment that HMR/TKT's HMR4396 infringed the '933 patent, the '698 patent, the '080 patent, the '349 patent, and the '422 patent. Amgen alleged infringement of claims 1, 2, and 9 of the '933 patent, claims 4-9 of the '698 patent, claims 2-4 of the '080 patent, claims 1, 3, 4, 6, and 7 of the '349 patent, and claim 1 of the '422 patent. See Amgen I, 126 F. Supp. 2d at 96–98. The case proceeded as outlined above and is again before us on appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

On this appeal, we are presented with issues relating to the '422, '080, '698, and '349 patents.[5] We begin with the '422 patent.

I.

The '422 Patent

Claim 1 is the only claim of the '422 patent at issue in the present case. Claim 1 provides:

> A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

'422 patent, col. 38, ll. 36-41.

HMR4396 already has been found to infringe claim 1 of the '422 patent. See Amgen II, 314 F.3d at 1320. In our remand instructions in Amgen II, we instructed the district court to construe the limitation "therapeutically effective amount" in claim 1 and then determine whether the Goldwasser reference or the Sugimoto patent anticipated claim 1 or whether the Sugimoto patent rendered claim 1 obvious.

A.

Claim Construction

On remand, the district court construed "therapeutically effective amount" in claim 1 of the '422 patent to require that the claimed EPO increase hematocrit and also be

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[5] As noted above, in Amgen II, we affirmed the ruling of the district court in Amgen I that claims 1, 2, and 9 of the '933 patent are invalid. Amgen II, 314 F.3d at 1342.

useful in healing or curing the class of patients listed at column 33, lines 22-28 of the specification of the '422 patent:

> A therapeutically effective amount is a quantity that produces a result that in and of itself helps to heal or cure. A therapeutically effective amount is one that elicits in vivo biological activity of natural EPO such as those listed in the specification, column 33, lines 24 through 28: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals.
>
> Therapeutically effective is to be interpreted as being therapeutically effective with respect to the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.

Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 245-46. In arriving at this construction, the district court focused on the portion of the specification of the '422 patent found at column 33, lines 11-28.[6] Id. at 232–36. The court also pointed to statements in the prosecution history asserting that the claimed invention of recombinant human EPO could be used to treat anemia and other similar disorders. Id. at 238–42.

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[6] The district court's claim construction references passages of the '933 patent found at column 33, lines 24-28 and column 33, lines 31-36. Id. at 214, 236, 245. The '422 patent contains identical passages at column 33, lines 16-20 and column 33, lines 23-28 respectively. These passages are part of a larger portion of the specification that runs from column 33, lines 11-28.

On appeal, HMR/TKT contends that the district court erred in construing the term "therapeutically effective" in claim 1 of the '422 patent by requiring that EPO increase hematocrit. HMR/TKT argues that the court incorrectly read the specification as limiting the scope of claim 1 to products that increase hematocrit. HMR/TKT urges that "therapeutically effective amount" means "an amount that elicits any of the biological effects listed in the specification." Under this construction, HMR/TKT asserts, claim 1 is anticipated by the Goldwasser reference.

Amgen responds that the district court correctly interpreted the specification to mean that "when a 'therapeutically effective amount' of EPO is used . . . it produces an increase in hematocrit—along with any or all of the biological affects [sic] previously attributed to natural EPO." Appellee's Br. 21 (quoting Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 234). Amgen points out that although the passage at column 33, lines 11-22 does not actually use the term "therapeutically effective," other passages do, in fact, use the term. For example, at column 33, lines 43-50, Amgen notes, the patent actually uses the words "therapeutically effective" before explaining the required dosages for patients. According to Amgen, this indicates that "therapeutically effective" amounts are those related to healing or curing disease. Amgen also directs our attention to the portion of the specification found at column 33, lines 22-28. This passage states, "Included within the class of humans treatable with products of the invention are patients generally requiring blood transfusions . . . and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like." According to Amgen, only amounts of EPO producing effects—particularly increased hematocrit—that counteract

these anemia-like diseases are "therapeutically effective." Amgen buttresses this argument with citations to the prosecution history where the patentee recounts the benefits of the claimed invention over prior art in treating disease.

The district court's claim construction is a matter of law, which we review de novo. Cybor Corp. v. FAS Techs.,138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). In Phillips v. AWH Corp., 415 F.3d 1303 (Fed. Cir. 2005) (en banc), we stated that claim construction must begin with the words of the claims themselves. Id. at 1312. A claim term has "the meaning that the term would have to a person of ordinary skill in the art. . . ." Id. at 1313. This meaning is ascertained "in the context of the entire patent, including the specification." Id. In particular, we stated in Phillips that "we must look at the ordinary meaning in the context of the written description and the prosecution history." Id. (quoting Medrad, Inc. v. MRI Devices Corp., 401 F.3d 1313, 1319 (Fed. Cir. 2005)). When dealing with technical terms, we noted, a court should look to "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." Id. (quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1116 (Fed. Cir. 2004)).

Using Phillips as a guide, we turn first to the language of the claims. Neither the language of claim 1, nor the language of claim 2, of the '422 patent offer any guidance as to the meaning of "therapeutically effective."[7] However, several passages of the

[7] Claim 2 is an independent claim, which provides: "A pharmaceutically-acceptable preparation containing a therapeutically effective amount of erythropoietin wherein human serum albumin is mixed with said erythropoietin." '422 patent, col. 38, ll. 42-44.

specification shed light on the meaning of the term. In particular, the text found at column 33, lines 11-22 states:

> [T]o the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals.

'422 patent, col. 33, ll. 11-22 (emphases added). This language indicates that the claimed invention is used in "therapy" to produce "any or all" of the following "effects": stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, stimulation of hemoglobin, and increasing hematocrit levels. Thus, increasing hematocrit is only one of the biological effects produced by the claimed invention. Accordingly, we agree with HMR/TKT that the district court misinterpreted this passage when it read it as limiting the claimed invention to products with "any or all" of the first four listed effects ascribed in vivo to EPO and also an increase in hematocrit.

Further, in the August 2, 1993 office action response, the patentee cited the above language of the specification and then stated, "It is believed that these sentences from the specification and others provide a clear and definite description of the uses for which the claimed erythropoietin compositions would be therapeutically effective." (emphasis added). Thus, the patentee interpreted the passage at column 33, lines 11-22 of the specification as listing the therapeutic effects of the invention disclosed in the '422 patent. We think the district court made an artificial distinction between the first

four effects listed in column 33, lines 11-22, stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, and stimulation of hemoglobin, and the fifth effect, an increase in hematocrit. The specification lists all five effects after stating that "any or all" of them may be an effect of therapy with the claimed invention. Thus, this section of the specification supports the construction that the '422 patent encompasses a pharmaceutical composition which produces "any or all" of the five listed effects.

As seen, the district court also determined that the specification indicates that the invention is limited to products that are "therapeutically effective" with respect to patients with anemia-like disorders, such as those listed at column 33, lines 22-28 of the '422 patent. Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 235–36, 245–46. For this determination, the court relied on a passage that recites several diseases that may be treated by the claimed invention. The passage begins, "Included within the class of humans treatable with products of the invention . . . ." '422 patent, col. 33, ll. 22-28. However, this passage does not state that the claims encompass only products that treat such patients. Rather, by using the non-limiting word "included," it suggests some persons, but not all persons, who may benefit from the invention.

Moreover, an additional section of the specification states, "It is noteworthy that the absence of in vivo activity for any one or more of the 'EPO products' of the invention is not wholly preclusive of therapeutic utility (see Weiland, et al., supra). . . ." Id. col. 36, ll. 9-12. We think the message of this passage is that "therapeutic utility" is not limited to products with "in vivo" effects. Thus, "therapeutic utility" is not dependent on the product having an effect in a living being, such as curing disease. Although this

passage relates to a different EPO product than the one disclosed in claim 1 of the '422 patent, we think it illustrates the broad meaning of "therapeutic utility" used throughout the '422 patent. It shows that the patentee did not use the word "therapy" in order to limit the scope of the '422 patent to only EPO that cured disease. Thus, products that are not necessarily effective in actually curing disease in humans are encompassed by claim 1 of the '422 patent. Based on a reading of the claims in light of the specification, it appears that the patentee used the words "therapeutically effective" in order to broadly claim a pharmaceutical composition with a wide range of effects. Those effects do not necessarily include curing disease in humans.

During the prosecution of the '422 patent, in an office action response filed October 23, 1997, the patentee noted that recombinant EPO, like that found in the claimed invention, "is the first therapeutic product which can be used to effectively treat hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts." In our view, this statement merely lists some of the uses of the invention, without restricting the scope of the invention.

In sum, we disagree with the district court's claim construction to the extent that it limits the scope of claim 1 of the '422 patent to EPO products that have one of the in vivo effects listed at column 33, lines 16-20 and that also increase hematocrit. We also disagree with the district court's conclusion that claim 1 of the '422 patent is limited to EPO products that may be used to treat patients with the disorders listed at column 33, lines 22-28 of the '422 patent's specification. On remand, the district court should utilize the following revised construction of "therapeutically effective:"

> A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals.

B.

Anticipation—The Goldwasser Reference

Based on its claim construction, the district court found in Amgen III Validity & Literal Infringement Judgment that the Goldwasser reference did not anticipate claim 1 of the '422 patent because Dr. Goldwasser's study was not effective in healing or curing. 339 F. Supp. 2d at 327. The parties dispute whether the Goldwasser reference anticipates claim 1 of the '422 patent under a revised claim construction. The purpose of the Goldwasser study was to examine EPO and its effects on erythropoiesis. Dr. Goldwasser acknowledged that mass production of EPO from recombinant DNA was not yet possible. Therefore, Dr. Goldwasser utilized EPO isolated from urine in an attempt to discover the chemistry and mode of action of EPO. In one portion of his study, Dr. Goldwasser performed a "very small clinical trial" using pure urinary EPO ("uEPO"). The uEPO was administered to three anemic patients. Two patients received injections of 520 units twice daily for ten days. The third patient received a 1000 unit injection every 2-3 days for three weeks. In his 1984 grant application, Dr. Goldwasser described the results of the clinical study as follows:

> There was no significant change in hematocrit in any patient; each patient, however[,] showed an increase in reticulocyte count, with peaks at 9, 10[,] and 11 days. The first two

> patients had increased erythroid cells in the marrow and an increased plasma iron clearance rate. One of the first two patients showed an increase in red cell mass. These fragmentary data, need to be reinforced with more extensive and extended studies but they show that epo can have a physiological effect in this type of anemia.

In Amgen I, the district court noted that Dr. Goldwasser testified that this "abortive, three-patient trial was a failure." 126 F. Supp. 2d at 112.

The district court found that the Goldwasser reference did not anticipate claim 1 of the '422 patent because none of the effects listed in Dr. Goldwasser's study included healing or curing within the court's construction of "therapeutically effective." Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 327–34. HMR/TKT argues that under a revised construction of "therapeutically effective" that broadens the scope of claim 1 to encompass EPO that "elicits any of the biological effects listed in the specification [at column 33, lines 16-22]," Dr. Goldwasser's study anticipates. Amgen counters that even under a broader construction of "therapeutically effective," Dr. Goldwasser's study does not anticipate claim 1 of the '422 patent because its recombinant EPO ("rEPO") product differs in structure and function from the uEPO utilized in Dr. Goldwasser's study. Amgen argues that a remand is not necessary because HMR/TKT admitted in its petition for a panel rehearing and rehearing en banc following Amgen II that the rEPO disclosed in claim 1 of the '422 patent differs in structure from naturally occurring uEPO.

Anticipation under 35 U.S.C. § 102 is a question of fact, which we review for clear error after a bench trial. Merck & Co., Inc. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1369 (Fed. Cir. 2003); Alza Corp. v. Mylan Labs., Inc., 391 F.3d 1365, 1369 (Fed.

Cir. 2004). The district court's factual findings on anticipation are clearly erroneous when "'although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.'" Merck & Co, 347 F.3d at 1369 (quoting United States v. U.S. Gypsum Co., 333 U.S. 364, 395 (1948)). A prior art reference anticipates a patent if it discloses all the limitations of the claimed invention. Oney v. Ratliff, 182 F.3d 893, 895 (Fed. Cir. 1999).

The district court's findings of fact on anticipation centered on whether the effects produced on patients in Dr. Goldwasser's study resulted in healing or curing. Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 327. Under our construction of "therapeutically effective," however, the district court's findings of fact as to "healing or curing," while relevant, do not end the anticipation inquiry. Additional findings of fact are necessary to determine whether the Goldwasser study anticipates under our new construction of "therapeutically effective." When findings of fact are necessary under a revised claim construction, it is appropriate for us to remand to the district court. See Seachange Int'l, Inc. v. C-Cor Inc., 413 F.3d 1361, 1381 (Fed. Cir. 2005) (remanding for the district court to consider anticipation after revising the claim construction). On remand, the district court should make findings of fact as to whether the Goldwasser reference meets the "therapeutically effective" limitation under our construction.[8]

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[8] If, on remand, the district court finds that the Goldwasser reference contains the "therapeutically effective" limitation, it must then determine whether the uEPO meets the other limitations of claim 1 of the '422 patent.

C.

Anticipation—The Sugimoto Patent

The Sugimoto patent, filed August 10, 1981, discloses a method for creating EPO-producing cells by creating hybrid cells from lymphoblastoids[9] and kidney tumor cells. The Sugimoto patent suggests using recombinant techniques to introduce the EPO genes from a human kidney tumor cell into human lymphoblastoids. Sugimoto patent, col. 1, l. 55–col. 2, l. 11. The patent involves in vivo production of EPO in which human lymphoblastoid cells capable of producing EPO are transferred to an animal body. The Sugimoto patent explains that the EPO produced by the animal according to this technique is then "collected easily by purification and separation techniques using conventional procedures . . . ." Id. col. 3, ll. 51-53.

In Amgen I, the district court found that the Sugimoto patent did not anticipate claim 1 of the '422 patent because it was not enabled. 126 F. Supp. 2d at 109. The court considered the testimony of Amgen's expert, Dr. Allan Erslev, who stated that the Sugimoto procedure was "very complex." Id. at 108. Dr. Erslev stated that no one had used the Sugimoto process prior to 1984, even though it would have been highly profitable if successful. Id. After recounting Dr. Erslev's testimony, the court discounted HMR/TKT's arguments. Id. HMR/TKT had put Dr. Michael Heartlein on the stand. By attempting to replicate the Sugimoto process, Dr. Heartlein produced cells that generated six times as much EPO as their parent cells. Id. at 108–09. The court found that Dr. Heartlein's experiments were not sufficient to show enablement, however,

[9] Lymphoblastoids are cells that are typically isolated from patients with leukemia, which is a cancer of the blood. Amgen I, 126 F. Supp. 2d at 106.